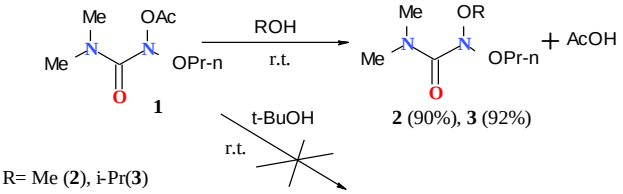
METHANOLYSIS OF *N*-ACETOXY-*N*-*n*-PROPYLOXY-*N*',*N*'-DIMETHYLUREA IN DIFFERENT CONDITIONS

Vasiliy Georgievich Shtamburg,[a] Alexandr Valerievich Tsygankov,[b] Victor Vasilievich Shtamburg,[c] Andrey Alexandrovich Anishchenko,[a]* Alexander Vladimirovich Mazepa[d] and Remir Grigorievich Kostyanovsky[e]

Keywords: nucleophilic substitution at nitrogen; *N*-acyloxy-*N*-alkoxyureas; *N*,*N*-dialkoxyureas; methanolysis.

The methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea in the presence of strong acids at room temperatures or in the boiling methanol yields *N*,*N*-dimethoxy-*N',N'*-dimethylurea as final product. Primarily the nucleophilic substitution acetoxy group at nitrogen on methoxy group arises. At second stage the transesterification of *N*,*N*-dialkoxyamino group of formed *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea take place.

* Corresponding Authors
Tel: +**380**-68-410-41-79
E-Mail: Koloxai@gmail.com
[a] Ukrainian State Chemico-Technologycal University, 49038 Ukraine, Dnepropetrovsk, Mostovaya st., 2/6.
[b] State Flight Academy of National Aviation University, 25013 Ukraine, Kirovograd, 50 Let Octiabrya,22/127
[c] Ukrainian State Chemico-Technologycal University, 61050 Ukraine, Kharkov, Moskovsky pr., 31/56.
[d] Bogatsky Physiko-Chemical Institute of NAS of Ukraine, 65063 Odessa, Armeyskaya st. 21 .107.
[e] Semenov Institute of Chemical Physics, Russian Academy of Sciences, 119991, Russian Federation, Moscow, Kosygina st., 4.



Scheme 1

INTRODUCTION

Amides,[2-9] carbamates,[10,11] and ureas,[10-15] having at nitrogen atom two electronegative substituents, one of them is alkoxy group and other substituent may be alkoxy group, acyloxy group, chlorine atom, 1-pyridinium group, are called "anomeric amides" due to $n_{O(Alk)} \rightarrow \sigma^*_{N-X}$ (X= OC(O)R, Cl, OAlk, $N^+C_5H_5$) anomeric effect domination. In X−N−O(R) group amide nitrogen is sp^3 hybridized and has pyramidal configuration, (Alk)O−N bond is shortened and N−X bond is elongated and destabilized. Due to this N−X bond destabilization the S_N2 nucleophilic substitution at amide nitrogen atom becomes possible.[2,4,6]

Earlier we had found that alcoholysis of *N*-acyloxy-*N*-alkoxyureas by primary and secondary alcohols at room temperatures (18-25 °C) yields the proper *N*,*N*-dialkoxyureas[7] (Scheme 1). If the methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** arises during 55 hours, the final isopropanolysis of compound **1** occurs during 1224 hours.[10] The *tert*-butanolysis of compound **1** no take place at room temperature because steric hindrances to the nucleophilic substitution at nitrogen,[10] realized, probably, via S_N2 mechanism.[2,4,6-8,10]

By alcoholysis at room temperatures *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** selectively converts in *N*,*N*-dialkoxyureas **2**,**3** and acetic acid. In these conditions acetic acid is indifferent to *N*,*N*-dialkoxyureas **2**,**3**.

But the influence of alcoholysis temperature and the presence of strong acids on the alcoholysis process remained practically unstudied.

EXPERIMENTAL

^{1}H NMR spectra were recorded on a Varian VXP-300 spectrometer (300 MHz, internal standard – Me_4Si), chemical shifts in σ-scale (ppm), coupling constants in Hz). Mass spectra were recorded on a VG-70EQ 770 mass spectrometer in FAB mode (FAB) and on Kratos MS 890 mass spectrometer electron impact mode (EI) and chemical ionization mode (CI), gas-reagent isobutane. MeOH was dried by boiling and distillation over Ca.

N-Acetoxy-N-n-propyloxy-N',N'-dimethylurea (1).[10]

Yellowish oil, n_D^{20} 1.4561. ^{1}H NMR (300 MHz, $CDCl_3$): 0.95 (t, 3H, $OCH_2CH_2\underline{Me}$, ^3J = 7.2 Hz), 1.68 (sex, 2H, $OCH_2\underline{CH_2}Me$, ^3J = 7.2 Hz), 2.15 (s, 3H, NO_2CMe), 3.04 (s, 6H, NMe_2), 4.04 (t, 2H, $O\underline{CH_2}CH_2Me$, ^3J = 7.2 Hz), IR (ν, $см^{-1}$): 1784 (C=O), 1732 (C=O). MS (CI, m/z (I_{rel}(%)): 206 $[M+2H]^+$ (17.3); 205 $[M+H]^+$ (100), 204 M^+ (9.4), 203 (11.9), 174 (15.3), 160 (16.0), 148 (10.8), 132 (25.8). Found (%): C 47.12, H 8.02, N 13.65. Calc. for $C_8H_{16}N_2O_4$ (%): C 47.05, H 7.90, N 13.72.

 DOI: 10.17628/ECB.2014.3.869

Methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea (1) in boiling MeOH.

The solution of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1,**[10] (3.95 mmol, 0.81 g) in MeOH (6 ml) was boiled for 4 h, than reaction mixture was evaporated *in vacuo*, the residue was distilled at 1 Torr, yielding 0.45 g (76 %) of *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4**, colorless liquid, bp. 98 – 99.5 °C (7 Torr), n_D^{20} 1.4470, identified with the reference sample of **2,**[10] by ^{1}H NMR. ^{1}H NMR (300 MHz, $CDCl_3$): 3.00 (s, 6H, NMe_2), 3.75 (s, 6H, $N(OMe)_2$).

***N*,*N*-Dimethoxy-*N',N'*-dimethylurea (4)**

N,N-dimethoxy-N',N'-dimethylurea (the reference sample) was obtained by methanolysis of *N*-acetoxy-*N*-methoxy-*N',N'*-dimethylurea,[10] at 20 °C for 34 h with yield 67 %.

***N*-Methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea (2)**.

Colorless oil, bp. 95-95.5 °C (1 Torr); n_D^{26} 1.4449, obtained by the methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** at 20 °C for 55 h with yield 80 %[10] and *n*-propanolysis of *N*-acetoxy-*N*-methoxy-*N',N'*-dimethyl-urea,[10] at 30 °C for 264 h with yield 82 %. ^{1}H NMR (300 MHz, $CDCl_3$): 0.96 (t, 3H, $CH_2CH_2\underline{Me}$, ^3J = 7.1 Hz), 1.67 (sex, 2H, $CH_2C\underline{H_2}Me$, ^3J = 7.1 Hz), 3.00 (s, 6H, NMe_2), 3.73 (s, 3H, NOMe), 3.91 (t, 2H, $NOCH_2$, ^3J = 7.1 Hz). MS (CI, m/z (I_{rel}(%)): 177 $[M+H]^+$ (7.7), 175 (6.4), 174 (9.9), 161 (32.8), 160 (11.0), 146 (14.0), 145 (19.0), 133 (11.2), 118 (13.9), 117 (46.5), 116 (29.3), 105 (12.9), 104 (24.3), 103 (40.2), 90 (14.3), 89 (100);, 73 (20.7), 72 (23.5). Found (%): C 47.82, H 9.17, N 15.63. Calc. for $C_7H_{16}N_2O_3$ (%): C 47.71, H 9.15, N 15.90.

Transesterification of *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea (2) by MeOH in the presence of AcOH.

The solution of *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **2** (0.500 mmol, 0.085 g) and AcOH (0.500 mmol, 0.030 g) in MeOH (1 ml) was boiled for 1 h, then MeOH was evaporated *in vacuo*, the residue was kept at 5 Torr and 23 °C, yielding 0.052 g (72 %) *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4**, identified by ^{1}H NMR.

Methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea (1) in the presence of CF_3CO_2H.

N-Acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** (1.474 mmol, 0.301 g) was added to solution of CF_3CO_2H (0.79 mmol, 0.09 g) in MeOH (4 ml). The reaction mixture was kept at 15 °C for 5 h, then MeOH was evaporated *in vacuo*, the residue was extracted by Et_2O (6 ml). Et_2O-Extract was evaporated *in vacuo*, the residue was kept at 2 Torr and 20 °C, yielding 0.214 g yellowish oil, which was identified by ^{1}H NMR as mixture of *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **2,**[10] and *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4** in molar ratio 69.8 %:30.2 % (molar). It means 60.5 % yield of urea **2** and 26.1 % yield of urea **4**.

Methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea (1) in the presence of oxalic acid.

N-Acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** (2.34 mmol, 0.60 g) was added to solution of oxalic acid (0.29 mmol, 0.03 g) in MeOH (4 ml). The reaction mixture was kept at 18-20 °C for 100 h, then MeOH was evaporated *in vacuo*, the residue was extracted by Et_2O (10 ml). Et_2O-Extract was evaporated *in vacuo*, the residue was kept at 1 Torr and 20 °C, yielding 0.31 g (71 %) *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4**, identified by ^{1}H NMR.

Transesterification of *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea (2) by MeOH in the presence of oxalic acid.

The mixture of *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **2,**[10] (0.466 mmol, 0.081 g), oxalic acid (0.052 mmol, 0.005 g) and MeOH (1 ml) was kept at 20 °C for 73 h, then MeOH was evaporated *in vacuo*, the residue was extracted by Et_2O (3 ml). Et_2O-Extract was evaporated *in vacuo*, the residue was extracted mixture of Et_2O (4 ml) and hexane (1 ml), the extract was evaporated *in vacuo*, the residue was kept at 5 Torr and 20 °C, yielding 0.045 g (66 %) of *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4**, identified by NMR ^{1}H.

Ethanolysis of *N*-acetoxy-*N*-methoxyurea (5) in boiling EtOH.

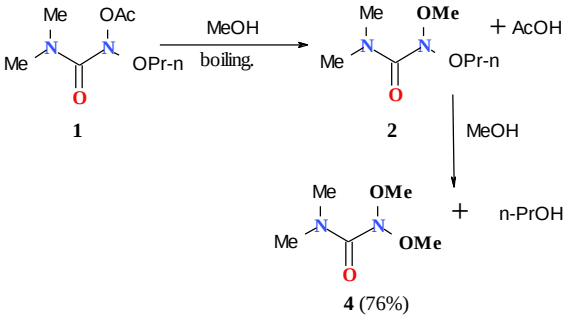
The solution of *N*-acetoxy-*N*-methoxyurea **5,**[11,16] (0.1601 mmol, 0.0237 g) in EtOH (4 ml) was boiled for 1 h, then EtOH was evaporated *in vacuo*, the residue was extracted by CH_2Cl_2 (3 ml), the CH_2Cl_2-extract was evaporated *in vacuo*, the residue was kept at 2 Torr and 20 °C, yielding 0.0172 g (80 %) of *N*-ethoxy-*N*-methoxyurea **6,** colourless oil**,** n_D^{20} 1.4493, identified by ^{1}H NMR and MS. ^{1}H NMR (300 MHz, $CDCl_3$): 1.33 (t, 3H, $NOCH_2\underline{Me}$, ^3J = 6.9 Hz), 3.84 (s, 3H, NOMe), 4.13 (q, 2H, $NO\underline{CH_2}Me$, ^3J = 6.9 Hz), 5.64 (br. s, 1H, NH), 5.96 (br. s, 1H, NH). MS (FAB, NaI, m/z (I_{rel} %)): 157 $[M+Na]^+$ (22), 89 $H_2NC(O)N^+OMe$ (25), 72 (77), 58 (100). Found (%): C 35.93, H 7.80, N 20.69. Calc. for $C_4H_{10}N_2O_3$ (%): C 35.82, H 7.51, N. 20.88. Also, *N*-ethoxy-*N*-methoxyurea **6** was obtained by ethanolysis of *N*-acetoxy-*N*-methoxyurea **5** at 15 °C for 69 h with yield 88 %.

Methanolysis of *N*-acetoxy-*N*-ethoxyurea (7) in boiling MeOH.

The solution of *N*-acetoxy-*N*-ethoxyurea **7,**[10,11] (0.925 mmol, 0.150 g) in MeOH (3.5 ml) was boiled for 4 h, then MeOH was evaporated *in vacuo*, the residue was extracted by CH_2Cl_2 (6 ml),the CH_2Cl_2-extract was evaporated *in vacuo*, the residue was kept at 2 Torr and 20 °C, yielding 0.089 g (72 %) of *N*-ethoxy-*N*-methoxyurea **6,** identified by ^{1}H NMR.

RESULTS AND DISCUSSION

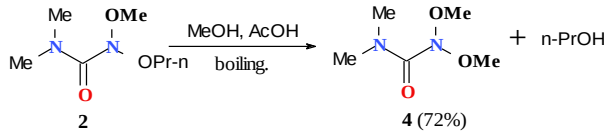
This work is devoted to study of the influence of conditions of alcoholysis of *N*-acyloxy-*N*-alkoxyureas on the nature of formed products. As we found the main product of methanolysis *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** in boiling methanol (4 h) was *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4** (Scheme 2).



Scheme 2

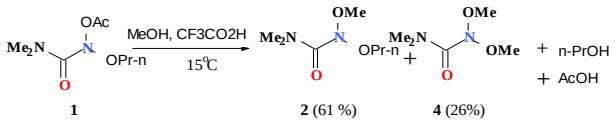
Probably, at the first stage *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **2** forms by nucleophilic substitution of acetoxy group at nitrogen in compound **1**. The weak signals of protons of urea **2** can be observed in ^{1}H NMR of reaction mixture. Then, at second stage, the transesterification of *N*,*N*-dialkoxyamino group of *N*,*N*-dialkoxyurea **2** by methanol arises yielding *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4**. Presumably the other product of propanolysis *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1**, acetic acid, catalyses this transesterification but only at boiling temperature (64 °C), not at room temperatures.[10] As was found earlier,[17,18] transesterification of *N*,*N*-dialkoxyamino group of *N*,*N*-dialkoxy-*N',N'*-dimethylureas,[17] and *N*,*N*-dialkoxy-*N*-*tert*-alkylamines,[18] took place by catalysis of more strong acids, such as TsOH.

This presumption is supposed by the independent transesterification of *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **2** to *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4** by the boiling of methanolic solution of compound **2** in the presence of acetic acid during 4 hours (Scheme 3)



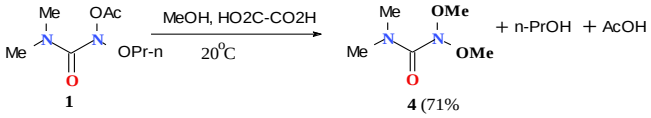
Scheme 3

We suggested that in the presence of acid, which is more strong than acetic aced, the secondary trasesterification will be occur at methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** at room temperature. Actually, it methanolysis in presence of trifluoroacetic acid at 15 °C for 5 hour yields the mixture of *N*,*N*-dialkoxyureas **2** and **4** in molar ratio 69.8 %:30.2 %. Respectively, yield of **2** is 61 %, yield of **4** is 26 %.



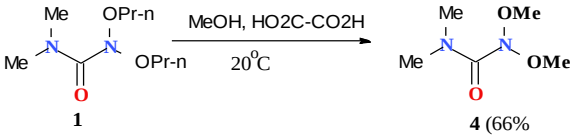
Scheme 4

In the presence of oxalic acid *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** converted by the methanolysis at 20 °C for 100 hour selectively in *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4** (Scheme 5). The traces of *N*,*N*-dialkoxyurea **2** are absent in the reaction mixture.



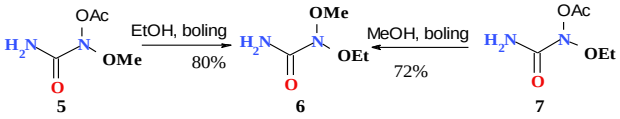
Scheme 5

Indeed, *N*-methoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **2** easily react with MeOH on the presence of oxalic acid (20 °C, 73 h), yielding *N*,*N*-dimethoxy-*N',N'*-dimethylurea **4** (Scheme 6)



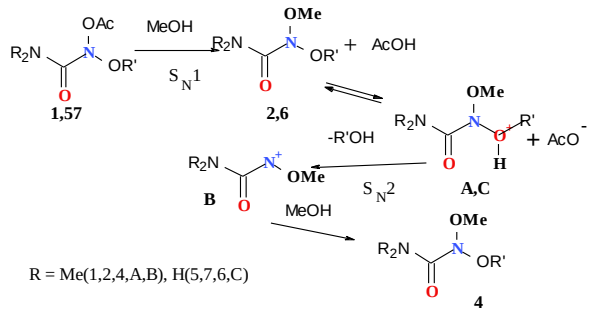
Scheme 6

Interestingly that for "unsubstituted" *N*-acetoxy-*N*-alkoxyureas **5**,**7** tranesterication of *N*,*N*-dialkoxyamino group in boiling alcohols in the presence of acetic acid don't take place (Scheme 7).



Scheme 7

This difference in the reactivity of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea **1** and *N*-acetoxy-*N*-alkoxyureas **5**,**7** can be understood on the assumption of S_N1 mechanism of transesterification *N*,*N*-dialkoxyamino group (Scheme 8). Earlier Glover has found that *N*-acetoxy-*N*-alkoxybenzamides underwent acid-catalyzed solvolysis by the $A_{Al}1$ (S_N1) mechanism.[2,4,19]



Scheme 8

At the first stage the nucleophilic substitution of acetoxy group by S_N2 mechanism,[2,4,6] take place. Then reversible O-protonation *N*,*N*-dialkoxyureas **2**,**6** arises. At the methanol boiling temperature protonated intermediate **A** (R=Me)

dissociates to nitrenium cation **B**, which reacts with methanol yielding *N*,*N*-dimethoxyurea **4**. The dimethylcarbamoyl moiety is only weakest electron-withdrawing substituent than methoxynitrenium cation **B** destabilization arises.

In the case of protonated intermediate **C** (R = H) it further dissociation to unstable methoxynitrenium cation becomes impossible because it carbamoyl moiety has substantial electron-withdrawing effect.

Thus methanolysis of *N*-acetoxy-*N*-*n*-propyloxy-*N',N'*-dimethylurea in the presence of strong acids at room temperatures or in the boiling methanol proceeds as two stage process yielding *N*,*N*-dimethoxy-*N',N'*-dimethylurea as final product.

Acknowledgement

This work was supported by the Russian Foundation for Basic Research (grant no. 13-03-90460) and Ukrainian Foundation for Fundamental Research (Grant no. F-53/105-2013).

References

[1]Shtamburg, V. G., Shishkin, O. V., Zubatyuk ,R. I., Shtamburg, V. V., Tsygankov, A. V., Mazepa, A. V., Kadorkina, G. K., Kostyanovsky, R. G., *Mendeleev Commun.*, **2013**, *23*, 289-291.

[2]Glover, S. A., *Tetrahedron*, **1998**, *54*, 7229-727.

[3]Gerdes, R. G., Glover, S. A., Ten Have, J. F., Rowbottom, C. A., *Tetrahedron Lett.*, **1989**, *31*, 5377-5380.

[4]Glover, S. A. Chapter 18. "*N-Heteroaton-substituted hydroxamic esters*" in "*The Chemistry of Hydroxylamines, Oximes and Hydroxamic Acids*", ed. Rappoport Z. and Liebman J. F., **2009**, John Wiley & Sons, Ltd.

[5]Gillson, A-M. E., Glover, S. A., Turner, D. J., Turner, P. *Org. Biomol. Chem.*, **2003**, *1*, 3430-3437.

[6]Cavanach, K. L., Glover, S. A., Price, H. L. Schumacher, R. R., *Aust. J. Chem.*, **2009**, *62*, 700 – 710.

[7]Digianantonio, K. M., Glover, S. A., Johns, J. P., Rosser, A. A., *Org. Biomol. Chem.*, **2011**, *9*, 4116-4126.

[8]Glover, S. A., White, J. M., Rosser, A. A., Digianantonio, K. M., *J. Org. Chem.*, **2011**, *76*, 9757 – 9763.

[9]Shtamburg, V. G., Tsygankov, A. V., Shishkin, O. V., Zubatyuk, R. I., Uspensky, B. V., Shtamburg, V. V., Mazepa, A. V., Kostyanovsky, R. G., *Mendeleev Commun.*, **2012**, *22*, 164-166.

[10]Shtamburg, V. G., Klots, E. A., Pleshkova, A. P., Avramenko, V. I., Ivonin, S. P., Tsygankov, A. V., Kostyanovsky, R. G., *Russ. Chem. Bull*, **2003**, *52*, 2251 – 2260.

[11]Shishkin, O. V., Zubatyuk, R. I., Shtamburg, V. G., Tsygankov, A. V., Klots, E. A., Mazepa, A. V., Kostyanovsky, R. G., *Mendeleev Commun.*, **2006**, *16*, 222-223.

[12]Shtamburg, V. G., Shishkin, O. V., Zubatyuk, R. I., Kravchenko, S. V., Tsygankov, A. V., Mazepa, A. V., Klots, E. A., Kostyanovsky, R. G., *Mendeleev Commun.*, **2006**, *16*, 323-325.

[13]Shtamburg, V. G., Shishkin, O. V., Zubatyuk, R. I., Kravchenko, S. V., Shtamburg, V. V., Distanov, V. B., Tsygankov, A. V., Kostyanovsky, R. G., *Mendeleev Commun.*, **2007**, *17*, 178-180**.**

[14]Shtamburg, V. G., Tsygankov, A. V., Gerasimenko, M. V., Shishkin, O. V., Zubatyuk, R. I., Mazepa, A. V., Kostyanovsky, R. G., *Mendeleev Commun.*, **2011**, *21*, 50-52**.**

[15]Shtamburg, V. G., Tsygankov, A. V., Shishkin, O. V., Zubatyuk, R. I., Shtamburg, V. V., Gerasimenko, M. V., Mazepa, A. V., Kostyanovsky, R. G., *Mendeleev Commun.*, **2012**, *22*, *92-94.*

[16]Shishkin, O. V., Shtamburg, V. G., Zubatyuk, R. I., Olefir, D. A., Tsygankov, A. V., Prosyanik, A. V., Mazepa, A. V., Kostyanovsky, R. G., *Chirality*, **2009**, *21*, 642 - 647.

[17]Rudchenko, V. F., Shevchenko, V. I., Kostyanovskii, R. G., *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1986**, *37*, 1436 – 1440.

[18]Rudchenko, V. F., Shtamburg, V. G., Pleshkova, A. P., Nasibov, Sh. S., Chervin, I. I., Kostyanovskii, R. G., *Bull. Acad. Sci. USSR Div. Chem. Sci.*, **1981**, *30*, 2100 – 2109.

[19]Campbell, J. J., Glover, S. A., Hammond, G. P., Rowbottom, C. A., *J. Org. Chem. Perkin Trans. 2*, **1992**, 2067 – 2079.

Received: 27.07.2014.
Accepted: 14.08.2014.